Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

Claim 1 (original): A method for predicting antisense activity of an oligonucleotide for down-regulating expression of a selected RNA comprising:

(a) developing an artificial neural network embodied on a computer-readable medium comprising

(I) constructing a database comprising sequence data of oligonucleotides tested *in vivo* for activity in down-regulating expression of RNAs and activity data corresponding to said sequence data,

(ii) providing an input layer containing a selected number of input nodes, optionally at least one hidden layer comprising a plurality of hidden nodes having full connectivity to said input nodes, and an output layer comprising at least one output node connected to said plurality of hidden nodes, if present, or to said input nodes,

(iii)   mapping sequence motifs of a preselected length found in the sequence data contained in the database, entering counts for each of said sequence motifs in selected input nodes of the input layer, and entering the activity data correlated with said counts of said sequence motifs, and

(iv) training the artificial neural network having the counts entered in the input layer thereof such that the artificial neural network produces an output in the output layer upon entry of sequence motif counts, wherein said output comprises a measure of predicted activity correlated with sequence motif counts for a test oligonucleotide; and

(b)   mapping sequence motifs of the preselected length present in a nucleotide sequence of a test oligonucleotide complementary to at least a portion of said selected RNA, determining counts of the mapped sequence motifs, and entering the counts of said sequence motifs present in the nucleotide sequence of said test oligonucleotide in the input layer of the artificial neural network; and

(c)   obtaining output of the predicted antisense activity of the test oligonucleotide for down-regulating expression of said selected RNA.

Claim 2 (original): The method of claim 1 wherein the sequence data in said database comprise sequence data compiled from published articles wherein each of said published articles reports results obtained with at least ten oligonucleotides and at least one mismatch or scrambled control oligonucleotide.

Claim 3 (withdrawn): The method of claim 1 wherein said input layer comprises one input node per sequence motif.

Claim 4 (previously presented): The method of claim 1 wherein said input layer comprises counts of only sequence motifs exhibiting a statistical correlation in their presence to oligonucleotide activity.

Claim 5 (withdrawn): The method of claim 4 wherein a χ^2 test for significance is performed on the sequence motifs for all oligonucleotide sequences in the database, such sequence motifs are ranked from most to least significant, and the selected number of input nodes corresponds to a selected number of most significant sequence motifs, one input node per most significant sequence motif.

Claim 6 (withdrawn):   The method of claim 5 wherein said selected number of most significant sequence motifs is about 20 to about 80.

Claim 7 (withdrawn):   The method of claim 6 wherein said number of most significant sequence motifs is about 40.

Claim 8 (original): The method of claim 1 wherein said at least one hidden layer comprises from about 4 to about 16 hidden nodes.

Claim 9 (withdrawn):   The method of claim 1 wherein said at least one hidden layer comprises about 4 hidden nodes.

Claim 10 (original):   The method of claim 1 wherein said output layer comprises one output node.

Claim 11 (withdrawn):   The method of claim 1 wherein said training the neural network further comprises using a back-propagation algorithm with a momentum term.

Claim 12 (original):   The method of claim 1 wherein said training the neural network further comprises using a back-propagation algorithm without a momentum term.

Claim 13 (previously presented):   The method of claim 1 further comprising reporting accuracy of predicted antisense activity by receiver operating characteristic (ROC) analysis.

Claim 14 (withdrawn):   The method of claim 1 further comprising assessing generalization of predicted antisense activity by minus 10% cross validation.

Claim 15 (withdrawn):   The method of claim 1 further comprising assessing generalization of predicted antisense activity by take-one-out cross-validation.

Claim 16 (withdrawn):   The method of claim 1 further comprising assessing generalization of predicted antisense activity by means of minus-one-RNA cross-validation.

Claim 17 (original):   The method of claim 1 wherein said counts of sequence motifs are entered as normalized data.

Claim 18 (currently amended): The method of claim 1 wherein said training comprises training with a ~~antisense activity of oligonucleotides is entered using a binary~~ threshold function ~~with a cutoff in the range of about 0.01-0.50~~.

Claim 19 (withdrawn):   The method of claim1 wherein discrimination of antisense activity of low-activity oligonucleotides is emphasized and antisense activity of high-activity oligonucleotides is de-emphasized.

Claim 20 (original):   The method of claim 1 further comprising combining the predicted antisense activity of the artificial neural network with a predicted antisense activity of at least one other artificial neural network.

Claim 21 (withdrawn):   The method of claim 1 further comprising combining the predicted antisense activity of the artificial neural network with an estimator of free-energy change associated with oligonucleotide-RNA duplex creation.

Claim 22 (original):   A method of making an artificial neural network, embodied on a computer-readable medium, for

predicting antisense activity of oligonucleotides for down-regulating expression of a selected RNA comprising:

(a)   constructing a database comprising sequence data of oligonucleotides tested *in vivo* for activity in down-regulating expression of RNAs and activity data corresponding to said sequence data;

(b)   providing an input layer containing a selected number of input nodes, optionally at least one hidden layer comprising a plurality of hidden nodes having full connectivity to said input nodes, and an output layer comprising at least one output node connected to said plurality of hidden nodes, if present, or to said input nodes;

(c)   mapping sequence motifs of a preselected length found in the sequence data contained in the database, entering counts for each of said sequence motifs in selected input nodes of the input layer, and entering the activity data correlated with said counts of said sequence motifs; and

(d)   training the artificial neural network having the counts entered in the input layer thereof such that the artificial neural network produces an output in the output layer upon entry of sequence motif counts, wherein said output comprises a measure of predicted activity correlated with sequence motif counts for a test oligonucleotide.

Claim 23 (original):   The method of claim 22 wherein the
sequence data in said database comprise sequence data compiled
from published articles wherein each of said published articles
reports results obtained with at least ten oligonucleotides and
at least one mismatch or scrambled control oligonucleotide.

Claim 24 (withdrawn):   The method of claim 22 wherein said
input layer comprises one input node per sequence motif.

Claim 25 (previously presented):   The method of claim 22
wherein said input layer comprises counts of only sequence motifs
exhibiting a statistical correlation in their presence to
oligonucleotide activity.

Claim 26 (withdrawn):   The method of claim 25 wherein a χ^2
test for significance is performed on the sequence motifs for all
oligonucleotide sequences in the database, such sequence motifs
are ranked from most to least significant, and the selected
number of input nodes corresponds to a selected number of most
significant sequence motifs, one input node per most significant
sequence motif.

Claim 27 (withdrawn):   The method of claim 26 wherein said selected number of most significant sequence motifs is about 20 to about 80.

Claim 28 (withdrawn):   The method of claim 27 wherein said number of most significant sequence motifs is about 40.

Claim 29 (original):   The method of claim 22 wherein said at least one hidden layer comprises from about 4 to about 16 hidden nodes.

Claim 30 (withdrawn):   The method of claim 22 wherein said at least one hidden layer comprises 4 hidden nodes.

Claim 31 (original):   The method of claim 22 wherein said output layer comprises one output node.

Claim 32 (withdrawn):   The method of claim 22 wherein said training the neural network further comprises using a back-propagation algorithm with a momentum term.

Claim 33 (original): The method of claim 22 wherein said training the neural network further comprises using a back-propagation algorithm without a momentum term.

Claim 34 (previously presented): The method of claim 22 further comprising reporting accuracy of predicted antisense activity by receiver operating characteristic (ROC) analysis.

Claim 35 (withdrawn): The method of claim 22 further comprising assessing generalization of predicted antisense activity by minus 10% cross validation.

Claim 36 (withdrawn): The method of claim 22 further comprising assessing generalization of predicted antisense activity by take-one-out cross-validation.

Claim 37 (withdrawn): The method of claim 22 further comprising assessing generalization of predicted antisense activity by means of minus-one-RNA cross-validation.

Claim 38 (original): The method of claim 22 wherein said counts of sequence motifs are entered as normalized data.

Claim 39 (currently amended): The method of claim 22 wherein said training comprises training with a ~~antisense activity of oligonucleotides is entered using a binary~~ threshold function ~~with a cutoff in the range of about 0.01-0.50~~.

Claim 40 (withdrawn): The method of claim 22 wherein discrimination of antisense activity of low-activity oligonucleotides is emphasized and antisense activity of high-activity oligonucleotides is de-emphasized.

Claim 41 (original): The method of claim 22 further comprising combining the predicted antisense activity of the artificial neural network with a predicted antisense activity of at least one other artificial neural network.

Claim 42 (withdrawn): The method of claim 22 further comprising combining the predicted antisense activity of the artificial neural network with an estimator of free-energy change associated with oligonucleotide-RNA duplex creation.

Claim 43 (original): An artificial neural network embodied on a computer-readable medium made by the method of claim 22.

Claims 44-64 (canceled)

Claim 65 (new):   The method of claim 1 wherein said training comprises training with direct activity data.

Claim 66 (new):   The method of claim 22 wherein said training comprises training with direct activity data.